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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/454,711	12/06/99	VAN BREE J	16994-012710

020350 HM12/0410
TOWNSEND AND TOWNSEND AND CREW
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EXAMINER	
PRATS,F	
ART UNIT	**PAPER NUMBER**
1651	8

DATE MAILED: 04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application N .	Applicant(s)	
	09/454,711	VAN BREE ET AL.	
	Examin r	Art Unit	
	Francisco C Prats	1651	

-- Th MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *See Continuation Sheet* .

Continuation of 20. Other: Notice to Comply With Sequence Requirements.

DETAILED ACTION

1. Claims 1-34 are presented for examination.

Election/Restrictions

2. Claims 27-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7, filed March 5, 2001.

3. Claims 1-26 are examined on the merits.

Compliance with Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). *See* page 27 of the specification, at lines 16-20, disclosing the six amino acid sequence AHPGRP appearing at the N-terminus of the disclosed α-glucosidase. Thus, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

While the sequences disclosed do not comply with the sequence rules cited above, the sequence is deemed non-essential to the examination of this application at this time because no sequence is recited in the claims. Applicant is therefore given the entire period for responding to this action to comply with the sequence rules. **FAILURE TO COMPLY FULLY WITH THE SEQUENCE RULES WITHIN THE RESPONSE PERIOD SET FOR THIS OFFICE ACTION WILL BE CONSIDERED AN INCOMPLETE RESPONSE.**

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1, 2, 6-10, 12, 14 and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Kikuchi et al (J. Clin. Invest. 101(4):827-833 (1998)).

Kikuchi discloses the treatment of Pompe's disease in quail

by administering to the quail patients, every 2-3 days for 18 days, by intravenous injection, 14 mg/kg body weight of recombinant human acid α-glucosidase in precursor form having 90% of the enzyme in the 110 kD form. Kikuchi also discloses the therapeutic efficacy of the treatment by disclosing that the administration results in normal histopathology in the heart and liver. Note that Kikuchi's enzyme would be indistinguishable from that produced in the milk of a transgenic animal. A holding of anticipation over the cited claims is therefore clearly required.

7. Claims 1, 4, 8-10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by de Barsy et al (Birth Defects, Original Article Series, Vol. IX, No.2, pages 184-190 (1973)).

The de Barsy reference discloses the treatment of Pompe's disease in a human infant patient by administering, in a single intravenous injection, 22 units of human acid α-glucosidase from placenta. Using the value of 7300 Units per mg protein on page 185, this means that about 3 mg of enzyme were administered to the patient. Assuming the infant weighed at least several kilograms, the administration rate was likely somewhere about 1 mg/kg. While the reference explicitly states that the treatment

resulted in no conspicuous morphologic or clinical improvements, it is noted specifically that liver enzyme concentration was improved over baseline from 32 to 142 hours after enzyme administration and that muscle enzyme concentration was improved at 149 hours after administration. Thus, the treatment in the reference can be considered as having had a therapeutic effect. A holding of anticipation over the cited claims is therefore required.

8. Claims 1, 8 and 9-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Reuser et al (U.S. Pat. 6,118,045).

Reuser discloses and claims a composition for the treatment of Pompe's disease in a human patient by intravenous injection, said composition comprising human acid α-glucosidase, obtainable from the milk of a transgenic animal. *See, e.g.,* claims 18-20 at col. 18. A holding of anticipation over the cited claims is therefore required.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (J. Clin. Invest. 101(4):827-833 (1998)), de Barsy et al (Birth Defects, Original Article Series, Vol. IX, No.2, pages 184-190 (1973)), and Reuser et al (U.S. Pat. 6,118,045) in view of Bijvoet et al (Biochim. Biophys. Acta 1308:93-96 (1996)) and Van Hove et al (Biochem. Mol. Biol Int'l. 43(3):613-623 (1997)).

As discussed above, each of Kikuchi, de Barsy and Reuser disclose the treatment of Pompe's disease by administering human acid α-glucosidase to patients in need thereof. Kikuchi, deBarsy and Reuser differ from the claims in that the dosage amounts disclosed therein are smaller than those recited in various embodiments recited in applicant's claims, and that the dosages

are not gradually increased as recited in some other embodiments in the claims.

However, de Barsy notes that the lack of significant clinical effects was likely due to the small amount of enzyme administered owing to lack of availability, and that the efforts disclosed therein must be considered preliminary. *See* p. 189, col. 1. Thus, de Barsy clearly suggests that increased dosage would be desirable in treating the disease. Moreover, each of Reuser (claims 18-20), Bijvoet (abstract at page 94, disclosing *in vitro* internalization of enzyme) and Van Hove (sentence spanning pages 613 and 614, disclosing endocytosis of 110 kD form of the enzyme and delivery to liver and heart upon injection) clearly suggest that relatively large amounts of the enzyme are obtained by the methods disclosed therein, and that the enzymes prepared therein are suitably targeted to the desired tissues, including muscle.

Thus, the artisan of ordinary skill, recognizing from de Barsy that high dosages would have been reasonably expected to improve the results disclosed therein, would have been motivated to have increased the enzyme dosage to the amounts recited in applicant's claims, suitable quantities of the enzymes being made available by the techniques disclosed in the Reuser, Bijvoet and Van Hove disclosures.

Moreover, the determination of a suitable dosage regimen, including the gradually increasing dosage regimen recited in the claims, clearly would have been a matter of routine optimization on the part of the artisan of ordinary skill, the determination of suitable treatment regimens being routinely determined in the pharmaceutical arts. Thus, absent some demonstration of an unexpected result, the claims must be considered obvious. In this regard note that the clinical trials described in the specification at pages 37-39 do not appear to present any significant data in that no clear results are presented. Therefore, it is respectfully submitted that no unexpected result has been demonstrated on the record.

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 703-308-3665. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Francisco C Prats
Primary Examiner
Art Unit 1651

FCP
April 9, 2001